REMARKS

Claims 44-74 were pending in this application when last examined. The Office Action cover page incorrectly indicates that claim 1, 2 and 14-49 are pending.

Claims 44-74 have been canceled and new claims 75-90 have been added. Each of new claims 75-89 relates to a vaccine composition or a method of producing a vaccine composition and each of new claims 75-89 should be included in the elected Group I. Also, claim 90 is directed a method of producing an immune response in a subject comprising administering the vaccine composition according to claim 75 to the subject, and should also be included in Group I.

Support for the amendments can be found in the specification and original claims as filed. No new matter has been added.

New claim 75 corresponds to subject matter of previous claims 44, 47, 50, 55, 57-59 and is further supported in the specification at page 2, lines 22-24; page 3, lines 6-7; and page 12, lines 3-4.

New claims 76-83 correspond to previous claims 45, 46, 48-51, 55 and 62.

New claims 84 and 85 correspond to subject matter of previous claims 44, 55 and 62.

New claim corresponds to subject matter of previous claims 47, 50, 55, 57-59, 63 and is further supported in the

specification at page 2, lines 22-24; page 3, lines 6-7; and page 12, lines 3-4.

New claims 87-90 correspond to previous claims 64-66 and 69.

ALLOWABLE SUBJECT MATTER

At page 9, the Office Action indicates that the prior art does not teach or suggest SEQ ID NOs 3 or 4. This would indicate that at least new claims 84 and 85 are free of the prior art and are directed to allowable subject matter.

OBJECTION TO SPECIFICATION

At page 4, the Office Action objects to the specification because it contains an embedded hyperlink. The amended specification removes the hyperlink.

CLAIM REJECTIONS - 35 USC § 112, FIRST PARAGRAPH

At page 4, the Office Action rejects claims 44-69, 73 and 74 under 35 U.S.C. § 112, first paragraph, written description requirement. Applicants respectfully traverse the rejection.

The Office Action acknowledges that the specification fully describes modifying an antigen-presenting cell (APC) to express a CD40L. The Office Action contends, however, that the specification does not disclose modifying an APC to express any

"cell-survival modulating molecule" as recited in the claims. The Office Action holds the position that the specification does not provide support for the genus of possible cell-survival modulating molecules which could include chemical compounds, nucleic acids, peptide or proteins.

The present claims further define the antigen-presenting cells. For example, new claims 75 and 84-86 specify that the antigen-presenting cells are modified to express CD40 ligand or GM-CSF encoded by a nucleotide sequence engineered into the cells. As recognized in the Office Action, the specification provides ample discussion for modifying the APC to express CD40L, (e.g., paragraphs [0142], [0143], [0147], [0163], [0165], [0171] and Figures 6, 8, 9, 11-13, 15, 17, 18, 20). The specification also fully describes APC modified to express GM-CSF (e.g., paragraphs [0141], [0143], [0157], [0163] and Figures 8, 12 and 13).

In view of the amendments and the above remarks, each of new claims 75-90 satisfies the written description requirements of 35 U.S.C. § 112, first paragraph. Accordingly, Applicants request reconsideration and withdrawal of the rejection.

CLAIM REJECTION - 35 USC § 102

At page 6, the Office Action rejects claims 44-47, 57, 60, 69, 73 and 74 under 35 U.S.C. § 102(b) as being anticipated

by KONTANI et al. (Cancer Gene Therapy (2002) 9:330-337). Applicants respectfully traverse the rejection.

These rejected claims were directed to a vaccine composition. New claim 75 is directed to a vaccine composition that includes a mixture of nucleotide sequence encoding an antigen and antigen presenting cells. The APCs are in the form of dendritic cells expressing toll-like receptor 9 and modified to express one of CD40 ligand and GM-CSF. Also, the nucleotide sequence is provided in a vector that includes unmethylated CpG sequence. KONTANI fails to teach or suggest such a vaccine.

KONTANI discloses the injection of non-primed dendritic cells (DCs) together with MUC1 DNA vaccine. The combination of DCs and DNA vaccine reportedly induces specific antitumor immunity in mice (see, Abstract). In contrast to the presently claimed vaccine composition, the two constituents are inoculated in separate injections (see, Vaccination paragraph at pages 331-332). The simultaneous and separate inoculation of the DCs and the antigen-encoding DNA is expected to increase the number of antigen-presenting cells (APCs) capable of priming T lymphocytes (see, Discussion paragraph at pages 335-336).

Thus, KONTANI fails to teach or suggest providing and using a mixture of an antigen-encoding nucleotide sequence and antigen-presenting cells. Furthermore, the antigen-presenting cells in KONTANI are non-primed and non-modified dendritic cells. KONTANI does not teach or suggest a vaccine composition that

includes antigen-presenting cells in the form of dendritic cells expressing toll-like receptor 9 and that are modified for expression of CD40 ligand or GM-CSF encoded by a nucleotide sequence engineered into the antigen-presenting cells. Finally, KONTANI also fails to disclose that the antigen-encoding nucleotide sequence is provided in a vector comprising a CpG sequence as featured in the present claims.

For at least these reasons, KONTANI fails to teach or suggest, and does not anticipate, the vaccine composition according to claim 75 and claims 76-83 dependent thereon. Accordingly, Applicants request reconsideration and withdrawal of the rejection.

CLAIM REJECTION - 35 USC § 103

At page 7, the Office Action rejects claims 48-56, 58, 59, 61 and 63-68 under 35 U.S.C. § 103(a) as being unpatentable over KONTANI along with KIKUCHI et al. (Blood (2000) 96(1):91-99) and KRUG et al. (European Journal of Immunology (2001) 31: 3026-3037.

At page 8, the Office Action rejects claim 62 under 35 U.S.C. § 103(a) as being unpatentable over KONTANI, KIKUCHI and KRUG, further in view of FRITZ et al. (WO 02/069900).

Applicants respectfully traverse these rejections and will address them together.

These rejected claims were directed to a vaccine composition and a method of producing a vaccine composition. As detailed in the above remarks, new claims 75-83 are directed to a vaccine composition. New claims 86-89 are directed to a method of producing a vaccine composition.

The Office Action acknowledges that KONTANI fails to teach or suggest modifying a plasmacytoid dendritic cell (previous claim 48) to express CD40L (previous claim 55) or adding an unmethylated CpG sequence to the nucleotide sequence (previous claims 59 and 61). The Office Action relies on KIKUCHI to teach modifying dendritic cells to express CD40L and KRUG to teach toll-like receptors on plasmacytoid dendritic cells for recognition of CpG motifs and the synergistic activation of plasmacytoid dendritic cells to produce immune response molecules such as IL-12 and IFN-α.

First, as detailed in the above remarks, KONTANI fails to teach or suggest a mixture of an antigen-encoding nucleotide sequence and genetically modified antigen-presenting cells. KONTANI discloses the separate administration of an antigen nucleotide sequence and non-modified antigen-presenting cells. KIKUCHI and KRUG fail to remedy this deficiency and indeed fail to teach any antigen-encoding nucleotide sequence.

KONTANI describes use of non-primed and non-modified dendritic cells and antigen-encoding nucleotide sequences for obtaining a vaccine composition to suppress tumor growth but

without any therapeutic efficacy for tumor elimination. The present application discloses a solution to how to provide a therapeutic vaccine composition capable of inducing systemic and tumor specific immunity protecting the host against tumor re-challenge. The vaccine composition according to the present claims involves mixing an antigen-encoding nucleotide sequence having a CpG sequence and gene-modified APCs. This mixing enhances the CTL-priming effect of the vaccine as compared to a separate administration of the two constituents (as taught in KONTANI). As detailed in the specification, vaccination with a vaccine as featured in the present claims induced superior therapeutic efficacy, eliminated pre-established tumors and achieved tumor-free mice. The vaccine also protected the tumor-free mice against tumor re-challenge when conducting tumor inoculation at a further distal site. (See, Fig. 15 and 17).

In distinction from the presently claimed vaccine, KONTANI discloses separate injection of a nucleotide sequence encoding antigen (MUC1 DNA) and nonprimed, syngeneic dendritic cells. Their vaccine composition can only induce a prophylactic vaccination (see, Fig. 3). No therapeutic vaccination is achieved. Indeed the KONTANI vaccine composition only reduced tumor growth when administered after tumor challenge and the tumors were still growing in the test animals, although at reduced rate as compared to control. (see, Fig. 4). Furthermore, survival of the test animals 50 days after tumor challenge was

very poor, with merely 20 % of the test animals being alive after the 50 day periods. This should be compared to the results disclose in the present application, which achieved 100 % test animal survival when administering a vaccine composition within the scope of the present claims following tumor challenge. (See, page 36, lines 11-32).

While KONTANI does not conduct any further experiments showing the effect of the vaccination in the case of a further tumor challenge, in this case, the animal survival would be even lower than 20 % because a single tumor inoculation resulted in such a high mortality. A further tumor re-challenge will consequently reduce the animal survival even further.

The Office Action appears to hold the position that one of ordinary skill in the art would combine the teachings of KONTANI with KIKUCHI and KRUG in order to improve on the KONTANI vaccine. In regard to KIKUCHI, positive results in terms of animal survival are only achievable with the vaccination in the case of direct injection of the CD40L-modified dendritic cells into the tumors (see, Figs. 2 and 3). Thus, when having tumors at two sites and only injecting the vaccine composition intratumorally for one of the two tumors, the survival rate dropped sharply and only 20 % of the test animals survived at 50 days following the tumor inoculation (see, Fig. 6).

One of ordinary skill in the art is well aware that for practical applications in human and animal patients, intratumoral

vaccination is not feasible. In clear contrast, systemic and therapeutic vaccination effect should be achieved regardless of the vaccination administration site relative the tumor site(s) in the human/animal body. Therefore, one would not have been led to apply the teaching of KIKUCHI to KONTANI when trying to design a vaccine composition that can induce systemic and tumor specific immunity even against tumor re-challenge. The reason for this is that based on the poor animal survival rates and vaccination efficacy of both KONTANI and KIKUCHI, one would not expect that a combination thereof would achieve any further advantageous effects or systemic and therapeutic immunity that not only eliminate the pre-existing tumors but also protects cured subjects against tumor re-challenge. It is also important to bear in mind that the methods of KONTANI and KIKUCHI developed to enhance immunostimulatory effects do not necessarily generate therapeutic effects, which is obvious from the inferior animal survival results presented in these documents.

Second, KONTANI and KIKUCHI fail to teach or suggest a nucleotide vaccine composition comprising a CpG sequence, or a vector comprising the antigen-encoding nucleotide sequence and a CpG sequence. KRUG discloses that plasmacytoid dendritic cells can be activated by incubation with CD40L and CpG oligonucleotides (see, Abstract). In KRUG, however, the CD40L and CpG oligonucleotides are simply added to a culture solution in which the plasmacytoid dendritic cells are present (see, section

2.1). The CpG sequence in KRUG is provided to antigen-presenting cells *in vitro* and not as part of a vector.

Furthermore, both KONTANI and KIKUCHI are directed towards compositions for tumor treatment. KRUG is directed towards potential beneficial effects in connection with intracellular pathogens, such as viruses, intracellular bacteria or parasites (see, Discussion section). The technical field of KRUG is not related to the technical field of KONTANI and KIKUCHI. Thus, one of ordinary skill in the art would not combine the teachings of a composition directed towards treatment of intracellular pathogens with an anti-tumor composition in order to improve the systemic and tumor specific immunity against tumor re-challenge.

For all of these reasons, the combination of KONTANI, KIKUCHI and KRUG fails to teach or suggest, and would not have rendered obvious, new claims 75-83 and 86-89. Accordingly, Applicants request reconsideration and withdrawal of the rejection.

In regard to previous claim 62, this claim featured a peptide of SEQ ID NO: 5 which the Office Action contended was disclosed in FRITZ. Claim 62 has been canceled and none of the new claims 75-90 specifically recite this peptide, thus rendering moot its rejection.

CONCLUSION

Entry of the above amendments is earnestly solicited. Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

Should there be any matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

Charge the fee of $110 for the one independent claim added herewith, to our credit card.

The Commissioner is hereby authorized in this, concurrent, and future submissions, to charge any deficiency or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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